DETAILED ACTION

Applicant's arguments filed 06/22/2009 have been fully considered. The amendment has been entered. Claims 1-42 are pending. Claims 1-22, 24-37 are withdrawn.

Claims 23, 38-42 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claim 23 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of applicant's arguments being convincing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23, 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Sanchez-Ramos et al,** (Experimental Neurology, 164: 247-256, 2000) in view of **Hutton et al,** (Clinical Biomechanics, 16: 728-734, 2001 (IDS)); **Hutton et al** (Spine, 24(15): 1507-1515, 1999 (IDS)); **Richardson et al,** (European Cells and Materials, 6:Suppl. 2, 20, 2003).

Sanchez-Ramos et al, teach human bone marrow stromal mesechymal stem cells (MSSCs) are induced to differentiate into neural cells under experimental culture conditions (abstract). Sanchez-Ramos suggests although BMSC express nestin, a commonly used marker of neural precursors, other cells may also transiently express these intermediate filaments (p 255, 1st column). The expression of one or even two neuronal proteins does not prove that the cell bearing these"neuronal markers" is capable of all the complex functions of a neuron. It will be important to determine whether longer incubation times result in more mature neuron-like cells and whether these cells possess functional and electrophysiological characteristics of neurons (p 255, 1st column). Sanchez-Ramos suggest understanding the molecular mechanisms responsible for neuronal differentiation of these cells will ultimately yield a readily available source of neural cells for cellular therapies ranging from gene therapeutics to neural reconstruction in neurodegenerative diseases, stroke, and trauma (p 255, 1st column). Sanchez-Ramos differs from the present invention for not teaching the MSSCs encapsulated in a gel to increasing pressures up to 30 psi and reduced oxygen pressure.

However, at the time the claimed invention was made, **Hutton et al,** (Clinical Biomechanics, 16: 728-734, 2001 (IDS)) teaches IVD cells exposed to specific values of hydrostatic pressure at 0.35 MPa and at atmospheric pressure (approximately 0.1 MPa) that hydrostatic pressure directly affects the synthesis of collagen and proteoglycan by the intervertebral disc cells (abstract). Hutton suggests the more useful comparison it would be to compare 1MPa with 0.35 MPa (figure 4 page 733 see comparison between 1MPa and 0.35 MPa) under reduced oxygen tension of 6% (p 734, 2nd column). Hutton suggest that in life the higher the pressure (1MPa) would tend to cause a fluid egress from the disc stimulates an increase in production of proteoglycans, these proteoglycans carry hydrophilic side chains, in other words, cells respond to higher pressure by producing more glycans, which have the

capacity to resist fluid loss (p 733, 2nd column bridge to p 734). **Hutton et al** (Spine, 24(15): 1507-1515, 1999 (IDS)) supplements the teachings of Hutton et al (2001) by teaching that further studies are needed to examine whether other values of hydrostatic pressure applied statically and cyclically also affects cell synthesis of the IVD cell collagen and proteoglycan markers and the consequence of applying high versus low pressure on the synthesis of collagen and proteoglycan on the disk cells (p 1514, 1st column, last paragraph). Hutton (1999) poses the question "is there is a window of hydrostatic pressure in which the disc cells function optionally" (p 1507, 2nd column, 2nd paragraph). Furthermore, Hutton (1999) teaches IVD cells in vivo are subjected to less than 3 MPa pressure (p 1507, 2nd column, 3rd paragraph). Hutton (1999) teaches that studies suggest a "physiological level of 0.3 MPa" of hydrostatic pressure acting as an anabolic factor because of the stimulation of the proteoglycan synthesis and TIMP-1 production may be essential for the maintenance of matrix (p 1507, 2nd column, last paragraph). Hutton (1999) also teaches that hydrostatic pressure of 2.5 MPa stimulated proteoglycan synthesis in the inner annulus of the human discs, in contrast 10 MPa inhibited proteoglycan synthesis (p 1508, 1st column, 1st paragraph). Hutton (2001) and Hutton (1999) differ from the present invention for not teaching the MSSCs encapsulated in a gel.

This deficiency is cured by **Richardson et al,** (European Cells and Materials, 6:Suppl. 2, 20, 2003) who teaches that adult human MSCs cultured in alginate gel were induced to differentiate along a chondrocytic phenotype, and MSCs may be used as a source of chondrocytes for repair of degenerate IVD (p 20 2nd column). Richardson teaches the use of human bone marrow mesenchymal stromal cells as a source of chondrocytes for treatment of intervertebral disc degeneration (title). As such, both Hutton (2001) and Hutton (1999) taken with Richardson provide sufficient motivation for one of ordinary skill in the art to expose the

cultured bone marrow MSSCs of Sanchez-Ramos/Risbud to increasing pressures of up to 2.5 MPa or up to 3 MPa induce differentiation toward IVD cells.

Accordingly, in view of the teachings of Hutton (2001)/Hutton (1999) and Richardson, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to apply increasing pressure up to 2.1 MPa as taught by Hutton (2001)/Hutton (1999) to the MSSCs of Sanchez-Ramos in order to yield differentiation of MSSCs towards IVD with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification in order to stimulate proteoglycan synthesis and collagen synthesis differentiation markers in order to differentiate MSSCs towards IVD cells by applying physiological levels of pressure as suggested by Hutton and Hutton. One of ordinary of skill in the art would have been particularly motivated to increase pressure up to 2.5- or 3 MPa since Hutton (1999) taught that hydrostatic pressure of 2.5 MPa stimulated proteoglycan synthesis in the inner annulus of the human discs, in contrast 10 MPa inhibited proteoglycan synthesis.

Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. at, 82 USPQ2d at 1395. Therefore, in view of Sanchez-Ramos/Hutton(2001)/Hutton(1999) and Richrdson it would be *prima facie* obvious for one of skill in the art to expose MMSCs to increasing pressures up to 2.1 MPa in order to stimulate synthesis of proteoglycan and collagen synthesis differentiation markers at physiological levels of pressure. Regarding optimization of reduced oxygen tension as instantly claimed one of ordinary skill in the art would have been sufficiently motivated to include different levels of reduced oxygen tension in order to affect proteoglycan synthesis in view of disclosure by Hutton (1999) that hydrostatic pressure of 2.5 MPa

stimulated proteoglycan synthesis in the inner annulus of the human discs, in contrast 10 MPa inhibited proteoglycan synthesis. In addition, It is evident that the person of ordinary skill would have optimized the oxygen pressure as a matter of design choice with reasonable expectation of achieving predictable results in human cells . One of ordinary skill in the art would have been sufficiently aware of these routine oxygen pressure optimization processes and would have used increments of oxygen pressure so as to include the instantly claimed increments in a human MSSC system in view of disclosure by both Hutton (2001) and Hutton (1999). One who would practice the invention would have had reasonable expectation of success because Richardson had already described use of use of human bone marrow mesenchymal stromal cells as a source of chondrocytes for treatment of intervertebral disc degeneration. Given that prior art teaches all the elements for causing human MSSCs to differentiate towards IVD cells it would have only required routine experimentation to apply to the MSSCs of Sanchez-Ramos encapsulated in a gel increasing pressures of up to 2.1 MPa and reduced increments of oxygen tension as taught by the combined cited references without undue experimentation.

The MPEP states that "A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330,

65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable there over because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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